## REMARKS

### Status of the Claims

This paper amends claims 28, 41, 46, and 50; cancels claims 43 and 52-68, and adds new claims 69-71. Support for the amendments is found generally in the Specification and, in particular, at [0011] and [0029]-[0030], [0042]-[0046] and in Figures 1 and 3. Support for new claim 69 is found, for example, at [0007] and support for new claims 70 and 71 is found at [0042]-[0046]. No new matter is added by these amendments. After the amendments set forth above are entered, claims 28-30 and 40-42, 44-51 and 69-71 are pending and under examination.

### Rejection under 35 U.S.C. § 112, second paragraph

Claims 46-49, 51, 62-65, and 67 stand rejected as indefinite. Specifically, the Examiner alleges that the linker "L" in the generic structure "TP-sugar-Px-L-Acr" of claim 46 is indefinite because it is not clear how and where the linker is attached to the acridinium moiety ("Acr"). Applicants respectfully traverse this rejection with respect to the pending claims and note that claims 62-65 and 67 are canceled.

In order to satisfy the definiteness requirement of section 112, the claims must "delineate the scope of the invention using language that adequately notifies the public of the patentee's right to exclude" Datamize, LLC v. Plumtree Software, Inc. 417 F.3d 1342, 1347 (Fed. Cir. 2005) (citing, Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1338 (Fed. Cir. 2003). "The definiteness requirement, however, does not compel absolute clarity. Only claims 'not amenable to construction' or 'insolubly ambiguous' are indefinite." Datamize at 1347 (citing, Novo Indus., L.P. v. Micro Molds Corp., 350 F.3d 1348, 1353 (Fed. Cir. 2003). "The perspective of a person of ordinary skill in the art at the time of the patent application governs the definiteness analysis. The definiteness of a patent claim depends on whether one skilled in the art would understand the bounds of the claim when read in light of the specification. Howmedica Osteonics Corp. v. Tranquil Prospects, Ltd., 401 F.3d 1367, 1371 (Fed. Cir.

2005)(internal citations omitted). Furthermore, claim breadth is not to be equated with indefiniteness. In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971).

As the Examiner correctly notes, the rejected claims place no particular limitation on the attachment of the linker to Acr. However, it is clear that the L-Acr attachment must not destroy the fluorescent property of Acr, rendering the compound unfit for its intended purpose. A skilled artisan can envision multiple suitable chemical linkages between the linker moiety and Acr. The Specification also provides several examples demonstrating specific L-Acr attachments (see, for example, Figures 1 and 3). Thus, the rejected claims are not "insolubly ambiguous" to the skilled artisan. To the contrary, the claims precisely define the Applicants' claimed structure. The Examiner appears to be objecting to the breadth of the claimed attachments rather than articulating sound reasoning supporting an indefiniteness rejection (MPEP 2173.04 "Breadth is not indefiniteness"). Applicants respectfully submit that this rejection is traversed and should be withdrawn.

**Rejection under 35 U.S.C. § 103(a)**

*Ebeie et al. in view of Furfine et al.*

Claims 28-30, 40-43, 45, 52-59, 61, and 68 stand rejected as being obvious over Eberie et al. (U.S. Patent 5,413,906) in view of Furfine et al. (WO 01/38587). The Examiner alleges that Eberie et al. teach a kit containing substantially the same reagents as required in Applicants' claimed invention. Office Action at page 5, first paragraph. The Examiner acknowledges, however, that Eberie et al. do not teach deoxynucleoside triphosphates (dNTPs) labeled with an acridinium moiety. Office Action at page 5, second paragraph. To remedy this deficiency, the Examiner alleges that Furfine et al. teach acridinium-labeled dNTPs and that it would have been obvious to use these labeled dNTPs in the kit of Eberie et al. Applicants respectfully disagree with respect to the pending claims.

The claims encompass a kit for determining RNA-dependent DNA polymerase activity comprising:

an RNA template;

a DNA primer complementary to a region of the RNA template and of length sufficient to form a stable template-primer hybrid molecule with the RNA template; and

a deoxynucleoside triphosphate labeled with an acridinium ester moiety;

wherein neither the RNA template nor the DNA primer contains a luminescent moiety and a solid phase for capturing a complex comprising the RNA template, DNA primer and the deoxynucleoside triphosphate labeled with acridinium ester moiety incorporated into the DNA primer by the polymerase.

In asserting this rejection, the Examiner fails to account for critical differences between the assay of Furfine et al., and that of Eberie et al. The primary Eberie et al. reference describes a polymerase activity assay which includes a template, at least one detectable mononucleoside triphosphate, at least one immobilizable mononucleoside triphosphate and a solid phase for capturing the immobilizable mononucleoside triphosphate. As acknowledged by the Examiner, Eberie et al. does not contemplate such a kit having a mononucleoside triphosphate labeled with an acridinium moiety.

The Examiner looks to Furfine et al., for a mononucleoside triphosphate with an acridinium moiety. Motivation to combine Eberie et al. with that of Furfine et al. however, is lacking because the later is directed to very different technology. As noted in the title of Furfine et al., the polymerase assay is a "continuous" time resolved polymerase activity assay that requires resonance energy transfer ("FRET"). The "continuous" time resolved assay by Furfine et al., provides measurement of polymerase activity in real time through its use of FRET. The Furfine et al. assay requires that both the primer-template complex and the dNTPs be labeled with energy-emitting chemical species. During the polymerase reaction, the sample is irradiated with an excitation wavelength specific for one of the energy-emitting chemical species. The detectable signal, indicative of polymerase activity, is produced by energy transfer from the

excited first chemical species (e.g., attached to the primer-template complex) to the second chemical species (e.g., attached to the dNTPs). Because this resonance energy transfer can occur only over a short distance, the labeled dNTPs must be incorporated into the labeled primer-template complex for a signal to be generated from the second energy-emitting species. See, for example, Furfine et al. at p. 4, ll. 10-25, p. 6, l. 17 through p. 7, l. 5 (but particularly p. 6, ll. 27-31), p. 12, ll. 5-11, and claim 1, step (d). As such, the signal coming from the second light-emitting chemical species in Furfine et al. is indicative of polymerization.

A kit for performing the Eberie et al. assay is necessarily much different from a kit for performing the Furfine et al. assay. The Eberie et al. assay does not use FRET and cannot be used for continuous monitoring of a polymerase assay. Therefore, the Eberie et al. assay does not require a primer template complex that contains an resonance energy emitting species as in Furfine et al. Furthermore, the "continuous" assay Furfine et al., made possible by the use of FRET, has no need or use for a solid phase, as described in Eberie et al. and required by the instant claims. Solid phase attachment of Eberie et al. is used after amplification, not during amplification as is the case in the "continuous" assay of Furfine et al. Eberie et al. needs a solid phase to separate labeled NTP incorporated by the polymerase from unincorporated labeled NTP. Thus, the assays Eberie et al. and Furfine et al. use fundamentally different approaches for monitoring fundamentally different outcomes and results. These differences are substantial and do not motivate their combination as asserted by the Examiner.

Furthermore, Applicant respectfully submits that, in formulating the rejection for alleged obviousness, the Examiner has erroneously relied upon improper hindsight reconstruction of the disclosure of the references in light of Applicants' teachings. It is well settled in patent law that the Examiner is not allowed to selectively pick and choose elements or concepts from the various references so as to arrive at the claimed invention using the claims as a guide. Hindsight is not a proper criterion for resolving the issue of obviousness. There is nothing in the art to support using the acridinium labeled NTP from Furfine et al. in the assay of Eberie et al. other than an improper hindsight reconstruction based on Applicant's disclosure. Furthermore, there is no

reasonable expectation of successfully using the acridinium labeled NTP from Furfine et al. in the absence of a FRET system such as taught by Eberie et al.

Accordingly, the rejection of claim 28 and the pending dependent claims is traversed and should be withdrawn.

*Eberie et al. in view of Furfine et al. and Nelson et al.*

Claims 44, 50, 60, and 66 stand rejected in view of Eberie et al. in view of Furfine et al., as alleged above, and in further view of Nelson et al. (Biochem. 35: 8429-8438, 1996). Applicants respectfully traverse this rejection with respect to the pending claims.

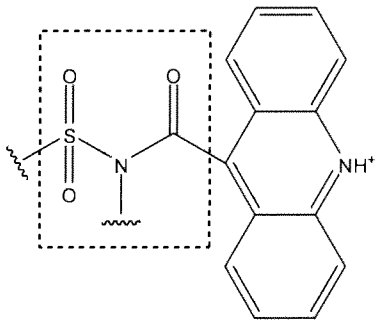
Nelson et al. do not provide what Eberie et al. and Furfine et al. lack. Whether or not Nelson et al. provide the particular acridinium species required in the rejected claims is irrelevant. Nelson et al. do not address the basic deficiency in the Examiner's combination of Eberie et al. and Furfine et al. as applied above. Nelson et al. merely provides additional species of chemiluminescent acridinium moieties. Even if one were motivated to incorporate the Nelson et al. acridinium species into the method of Furfine et al., the incorporation would be a mere substitution of one moiety for the other. Nothing in Nelson et al. suggests altering the basic FRET assay of Furfine et al. Accordingly, the rejection of claims 28 and the pending dependent claims is traversed and should be withdrawn.

*Eberie et al. in view of Celebuski et al.*

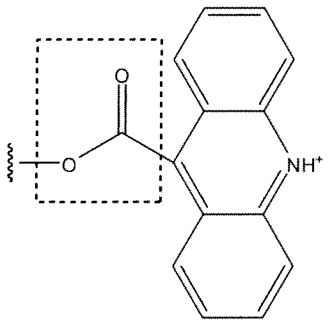
Claims 28-30, 40-46, 52-62, and 68 stand rejected in view of Eberie et al. in view of Celebuski et al. (EP 0407816). The Examiner alleges that Eberie et al. teach a kit containing substantially the same reagents as required in Applicants' claimed invention, but acknowledges that Eberie et al. do not teach deoxynucleoside triphosphates (dNTPs) labeled with an acridinium moiety. Office Action at page 9, second paragraph. To remedy this deficiency, the Examiner alleges that Celebuski et al. teach base-modified nucleosides which conform to the formula:

TP-sugar-Px-L-Acr, as defined in the rejected claims. Applicants respectfully traverse this rejection with respect to the pending claims

Applicants' claimed kit encompasses dNTPs labeled with acridinium moieties different than those disclosed by Celebuski et al. Specifically, as shown in Figure 8 and Example 8, the acridinium moieties of Celebuski et al. are acridinium sulfonamides having the following basic structure:




In contrast, Applicants' claimed acridinium moieties are acridinium esters:




Thus, Celebuski et al. is concerned with a different chemical class of acridinium moieties not encompassed by the rejected claims. This renders Celebuski et al. irrelevant to Applicants' claimed invention. Accordingly, this rejection is traversed and should be withdrawn.

*Eberie et al. in view of Celebuski et al. and Petrie et al.*

Claims 47-49 and 63-65 stand rejected over Eberie et al. in view of Celebuski et al., as alleged above, and in further view of Petrie et al. (U.S. Patent 5,824,796). Applicants respectfully traverse this rejection with respect to the pending claims.

Petrie et al. do not provide what Eberie et al. and Celebuski et al. lack. Whether or not Petrie et al. provide chemical linkers similar to those specified in claims 47-49 and 63-65 is irrelevant. Petrie et al. do not address the basic deficiency in the Examiner's combination of Eberie et al. and Celebuski et al. (i.e., the use of acridinium esters). Accordingly, this rejection is traversed and should be withdrawn.

*Eberie et al. in view of Celebuski et al. and Nelson et al.*

Claims 44, 50-51, 60, and 66-67 stand rejected in view of Eberie et al. in view of Celebuski et al., as alleged above, and in further view of Nelson et al. Applicants respectfully traverse this rejection with respect to the pending claims.

As discussed above, the teachings of Celebuski et al. are irrelevant to the rejected claims because Celebuski et al. are concerned with acridinium sulfonamides, whereas Applicants' claimed invention encompasses only acridinium esters.

Applicants submit that the combination of Eberie et al. and Nelson et al. do not render obvious the claimed invention for the reasons of record. Nelson et al. merely identifies a variety of acridinium moieties, but does not provide any instruction relevant to their use in labeleing dNTPs in a polymerase detection assay. Specifically, Nelson et al. merely provide a method for the post-synthetic labeling of oligonucleotide probes (see, p. 8431, right column, second full paragraph). This method is incompatible with the Eberie et al. detection assay. Accordingly, this rejection is traversed and should be withdrawn.

## CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to contact the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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